Clinical Investigation

Hormone Replacement Therapy Is Safe in Women Undergoing Coronary Artery Bypass Grafting

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In postmenopausal women, hormone replacement therapy (HRT) does not substantially reduce the incidence of cardiovascular disease and may produce a short-term increase in risk. Therefore, we investigated whether HRT increased risk in patients with severe coronary artery disease necessitating surgery.

We prospectively studied 4,782 patients undergoing coronary artery bypass grafting at 70 centers in 17 countries from November 1996 through June 2000. Patients were selected using a systematic sampling technique. Mortality, major morbidity, and transfusion requirements were compared among 3 groups: men (n=3,840), women receiving HRT (n=144), and women not receiving HRT (n=798).

Women actively receiving HRT, compared with women not receiving HRT or with men, were at no greater risk of developing the following fatal or non-fatal complications: death (2.8% vs 4.4% vs 2.8%, respectively; P=0.05), myocardial infarction (6.3% vs 7.0% vs 7.7%; P=0.67), central nervous system complication (2.1% vs 2.8% vs 2.9%; P=0.85), or renal dysfunction (0.7% vs 5.3% vs 4.8%; P=0.06). Incidence of postoperative congestive heart failure was significantly lower in men (7.7%) than in women receiving HRT (12.5%; P=0.04) and in women without HRT (12.8%; P <0.0001). Fewer men (61%) needed red blood cell transfusion than did women receiving HRT (79%) and women without HRT (88%) (P <0.0001 compared with both other groups). However, the need for fresh frozen plasma transfusions was significantly less in women receiving HRT (16%) than in women not receiving HRT (25%; P=0.01). We conclude that HRT administration before coronary artery bypass grafting does not increase women's risk of any adverse outcome. ***(Tex Heart Inst J 2005;32:507-14)***

Key words: *Coronary artery bypass; estrogen replacement therapy; female; hormone replacement therapy; male; mortality rate; postoperative complications; sex factors; transfusion, blood; treatment outcome*

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Considerable debate exists about whether women's higher risk of morbidity and mortality after coronary artery bypass grafting (CABG) is due to female sex per se or to the tendency for women to be diagnosed with heart disease at a later age, when they have more unfavorable risk factors.[1-4] Although most women undergoing CABG are postmenopausal, few studies have explored the possible role of hormone replacement therapy (HRT) in the outcomes of these patients.[5-7] Several large, prospective, randomized trials investigating the effects of long-term HRT in women with and without coronary artery disease have failed to show significant beneficial effects in primary or secondary prevention of atherosclerotic disease.[8-10] Most recently, the Women's Health Initiative found that women taking estrogen with or without progesterone had a slightly elevated risk of adverse coronary events.[11-13]

The setting of acute surgical intervention for coronary artery disease, including cardiopulmonary bypass and possibly inadequate myocardial protection during bypass, ischemia-reperfusion injury of the myocardium, and perioperative hemodynamic instability, is different from the setting of long-term primary or secondary prevention of disease. Several clinical studies suggest that HRT in postmenopausal women favorably affects outcome after the endoluminal trauma of acute myocardial infarction[14] and coronary angioplasty.[15,16] We also have shown, in a single-center study of CABG patients aged 55 years or more, that women receiving preoperative HRT had a significantly lower in-hospital mortality than did women who were not receiving HRT.[5] Furthermore, many potentially beneficial cardiovascular and non-cardiovascular effects of estrogen have been described.[17] Therefore, we used data gathered prospectively in an international multicenter study to evalu-

ate the effects of HRT on mortality and morbidity after CABG in women.

Patients and Methods

Study Design and Patients

Studies were performed in compliance with the human-studies guidelines and welfare regulations of the authors' institutions, and informed consent was obtained from the patients. The Multicenter Study of Perioperative Ischemia Epidemiology II, funded by the Ischemia Research and Education Foundation, is a prospective longitudinal study of 5,436 patients who underwent CABG at 70 hospitals in 17 countries from November 1996 through June 2000. Each center used a systematic sampling scheme to select 100 patients aged 18 or older who were undergoing CABG with or without valve repair or replacement while on cardiopulmonary bypass. Of the 5,436 patients enrolled, 371 were excluded from the data analyses because of patient withdrawal (n=32), death before surgery (n=2), canceled or rescheduled surgery (n=97), alteration of surgical schedule (n=132), enrollment in another study (n=11), or incomplete data collection (n=97). Also excluded were 256 patients who had additional surgical procedures concurrent with CABG (other than valve repair or replacement) and 27 female patients whose use of HRT medication was not recorded. Therefore, a total of 4,782 patients were included in the analyses.

Data Collection and Management

Collected data included demographic, historical, clinical, laboratory, and electrocardiographic information, as well as resource use and adverse outcomes. All data fields for each patient were queried for completeness and accuracy, with all changes documented before database closure. All outcomes were defined in advance and determined by independent investigators blinded to the study question.

For the women, preoperative questions regarding menopause included the following:

1) How old were you when you stopped having regular natural periods?
2) Have you ever received estrogen replacement medication?
3) Are you currently receiving estrogen replacement medication?
4) How many years have you taken estrogen replacement therapy?

All analyses involved 3 groups: women currently receiving HRT, women not receiving HRT, and men. Group membership was the primary predictor variable. We also examined the predictive value of other preoperative variables, including age, body mass index, history of congestive heart failure (CHF), diabetes (with or without insulin dependence), hypertension, unstable angina, myocardial infarction (MI), stroke, history of carotid artery disease, history of peripheral vascular disease, chronic obstructive pulmonary disease, valve disease, previous heart surgery, urgent surgery, and preoperative intra-aortic balloon pump placement. The potential influence of additional preoperative medications, including angiotensin-converting enzyme inhibitors, β-blockers, calcium channel blockers, antihyperlipidemic agents, and aspirin, was also analyzed. Potential intraoperative predictor variables included duration of cardiopulmonary bypass, duration of aortic cross-clamping, and use of an internal mammary artery (IMA) graft.

The primary outcome variable was in-hospital mortality. Secondary outcome variables included new major postoperative morbidity, such as MI, CHF, central nervous system complication, and renal dysfunction. A postoperative diagnosis of MI was made if there were new Q waves (Minnesota codes[18] 1-1-1 to 1-2-7), new persistent ST-segment or T-wave changes (Minnesota codes 4-1, 4-2, 5-1, 5-2, or 9-2), elevated values for the myocardial band isoenzyme of creatine kinase (according to each institution's guidelines), or evidence of acute MI on autopsy. A diagnosis of CHF was made if a ventricular assist device was used, if continuous inotropic support was required for at least 24 hours, or if there was evidence of heart failure on autopsy. A central nervous system complication was defined as neurologic death, new overt postoperative stroke, new transient ischemic attack, or encephalopathy, coma, or stupor at the time of hospital discharge. Postoperative renal dysfunction was defined as a postoperative serum creatinine increase of at least 0.70 mg/dL to a level of at least 2.0 mg/dL, new postoperative dialysis, or evidence of renal failure on autopsy. For each patient, total chest tube output was recorded, and total intraoperative and postoperative use of blood products was examined, including the use of red blood cell (RBC) products (defined as the use of either whole blood or packed red cells), fresh frozen plasma (FFP), and platelets. The duration of postoperative hospitalization was also recorded for each patient.

In a post hoc analysis of mortality and major morbidity, women not currently receiving HRT were further divided into 2 subgroups: women who had never received HRT and women who had discontinued previous use of HRT.

Statistical Methods

For categorical variables, 2-tailed χ^2 or Fisher exact tests were used to compare patients in the 3 groups. For continuous variables, *t* tests or Wilcoxon rank sum tests were applied. Because 3 tests were performed for each dependent variable (1 for each possible pair of groups), Bonferroni correction was used. All predictor

variables that were significant at a 2-tailed nominal *P* value of less than 0.15 in univariate analyses were then entered into a stepwise logistic regression analysis designed to predict postoperative mortality or survival. Variables were retained if they were significant at a 2-tailed nominal *P* value of less than 0.05. When Bonferroni correction for multiple testing was performed, a *P* value of less than 0.017 was considered significant. All analyses were performed using SAS software, version 8.12 (SAS Institute, Inc.; Cary, NC).

Results

Of the 4,782 patients included in the study, 942 were women, 144 of whom (15.2%) were receiving HRT at hospital admission. Women receiving HRT had taken their medication for a mean of 10.0 ± 9.7 years before surgery, ceased having regular natural periods at 44.2 ± 8.2 years of age, and had a duration of menopause of 19.5 ± 11.0 years. Women not receiving HRT had ceased having regular natural periods at 47.0 ± 6.1 years of age (*P* <0.0001 vs women with HRT) and had a duration of menopause of 21.5 ± 9.7 years (*P* <0.03 vs women with HRT).

Preoperative patient characteristics, intraoperative data, and length of hospital stay were compared among the 3 groups (Table I). Women not receiving HRT were significantly older (*P* <0.0001), less likely to have received postgraduate education (*P* <0.0001), and less likely to receive an IMA graft (*P* <0.007) compared with women receiving HRT or with men. Women receiving HRT were more likely to be obese (*P* <0.002) and less likely to have received preoperative β-blockers (*P* <0.02) than were men (Table I).

The in-hospital mortality rate for all patients was 3.1%. The mortality rate was lower in men (2.8%) compared with women not receiving HRT (4.4%) (*P*=0.023), but not compared with women receiving HRT (2.8%). However, multivariate analysis indicated no significant differences between men and either group of women (Table II).

There were no significant intergroup differences in the incidence of postoperative MI (Table III). However, men had a significantly lower incidence of postoperative CHF than did women not receiving HRT (*P* <0.0001). There were no significant intergroup differences for any other adverse outcome except for renal dysfunction, which was less frequent in women receiving HRT (*P* <0.0001 vs women not receiving HRT and *P* <0.02 vs men). However, in a stepwise logistic regression, neither male sex nor HRT status in women was independently predictive of any adverse outcome except for the lower incidence of postoperative CHF in men (*P* <0.05).

Resource use was measured by transfusion incidence and length of hospital stay (Table III). Each group differed significantly from the other two in terms of the incidence of RBC transfusion (88% in women not receiving HRT, 79% in women receiving HRT, and 61% in men; *P* <0.0001 for all comparisons). Furthermore, analysis of the number of RBC units transfused

TABLE I. Patient Characteristics (N=4,782)

Characteristic	Women Receiving HRT: Yes (n=144)	Women Receiving HRT: No (n=798)	Men (n=3,840)
Age (yr)	63.1 ± 8.6	67.2 ± 9.6*	63.3 ± 9.7
Obesity (body mass index >28 kg/m²) (%)	53	42	39†
Diabetes (%)	42	38	29*
Postgraduate education (%)	20	7*	20
History of:			
Congestive heart failure (%)	46	45	34*
Myocardial infarction (%)	54	59	64*
Neurological event (%)	17	12	10
Hypertension (%)	76	77	65*
Peripheral vascular disease (%)	20	20	16‡
Renal insufficiency (%)	9	7	8
Valve disease (%)	29	30	19*
Chronic obstructive pulmonary disease (%)	15	11	12
Smoking			
Current smoker (%)	19	8	11
Ex-smoker (%)	43	38	63*
Never smoked (%)	38	54	26*
Preoperative use of ACE inhibitors (%)	45	47	43
Preoperative use of β-blockers (%)	59	68	69†
Preoperative use of calcium channel blockers (%)	47	39	35
Preoperative insertion of IABP (%)	0.7	1.1	1.2
Redo operative status (%)	8	5	8‡
Concomitant procedure (%)	15	16	9‡
>3 vessels bypassed (%)	24	21	28‡
Use of an internal mammary artery graft (%)	87	77*	87
Duration of cardiopulmonary bypass (min)	100 ± 43	101 ± 40	103 ± 43

ACE = angiotensin converting enzyme; HRT = hormone replacement therapy; IABP = intraaortic balloon pump

Values are presented as mean ± standard deviation; *$P \leq 0.01$ vs both other groups; †$P \leq 0.01$ vs women receiving HRT; ‡$P \leq 0.01$ vs women not receiving HRT.

TABLE II. Multivariate Predictors of Mortality and Survival after Coronary Artery Bypass Grafting

	Odds Ratio	95% CI	*P* Value
Predictors of mortality			
Preoperative IABP insertion	3.4	1.5, 7.7	0.003
History of renal insufficiency	2.7	1.8, 4.1	<0.0001
Redo operative status	2.6	1.6, 4.2	0.0002
History of valve disease	1.9	1.3, 2.7	0.0007
History of congestive heart failure	1.7	1.2, 2.5	0.004
Age >70 years	1.7	1.2, 2.4	0.005
Preoperative use of ACE inhibitors	1.7	1.2, 2.4	0.004
Women without HRT vs women with HRT	0.7	0.2, 2.1	0.51
Women without HRT vs men	0.8	0.5, 1.2	0.30
Women with HRT vs men	0.9	0.3, 2.5	0.79
Predictors of survival			
Use of an internal mammary artery graft	0.7	0.5, 1.0	0.004
Postgraduate education	0.5	0.3, 0.9	0.02

ACE = angiotensin converting enzyme; CI = confidence interval; HRT = hormone replacement therapy; IABP = intra-aortic balloon pump

TABLE III. Postoperative Outcomes and Resource Use

	Women Receiving HRT		
Outcome	**Yes** (n=144)	**No** (n=798)	**Men** (n=3,840)
Myocardial infarction (%)	6.3	7.0	7.7
Congestive heart failure (%)	12.5	12.8	7.7†
CNS complication (%)	2.1	2.8	2.9
Renal dysfunction (%)	0.7†	5.3	4.8
RBC transfusion (units)	3.7 ± 2.9	4.2 ± 3.5	3.8 ± 4.4*
RBC transfusion (%)	79†	88†	61†
FFP transfusion (units)	5.6 ± 4.6	4.9 ± 6.5	4.8 ± 6.8
FFP transfusion (%)	16*	25†	21
Platelet transfusion (units)	7.0 ± 5.6	7.5 ± 6.7	6.6 ± 6.8
Platelet transfusion (%)	16	17	15
Chest tube output (mL)	740 ± 637	678 ± 672	777 ± 636*
Duration of hospital stay (days)	9.7 ± 6.3	11.0 ± 8.7†	9.9 ± 7.6

CNS = central nervous system; FFP = fresh frozen plasma; HRT = hormone replacement therapy; RBC = red blood cell

Values are presented as mean ± standard deviation. *$P \leq 0.01$ vs women not receiving HRT; †$P \leq 0.01$ vs both other groups.

revealed that men received significantly fewer units than did women not receiving HRT ($P < 0.002$). However, multivariate analysis did not confirm any significant differences between groups in the incidence of RBC transfusion or in the number of RBC units transfused.

There were no significant differences in the incidence of platelet transfusion or the number of units transfused. However, perioperative FFP transfusions were less frequent in women receiving HRT than in women not receiving HRT or in men ($P < 0.01$; Table III). Multivariate analysis confirmed a lower incidence of FFP transfusion in women receiving HRT than in women not receiving HRT ($P < 0.02$). Women without HRT had significantly longer postoperative hospital stays than did men ($P < 0.0001$) or women receiving HRT ($P < 0.004$). However, multivariate analysis indicated that neither sex nor HRT status independently predicted duration of hospital stay.

In a post hoc analysis of mortality and major morbidity rates, women not currently receiving HRT were further divided into 2 subgroups: women who had never received HRT and women who had discontinued previous use of HRT. These analyses showed that in-hospital mortality was 4.1% for women who had never received HRT (n=690) and 6.5% for women who had previously received HRT (n=108), compared with 2.8% for women currently receiving HRT (n=144) (P=0.34 for women currently receiving HRT vs both other groups).

Discussion

We found no effect of HRT administration on mortality or morbidity rates in women undergoing CABG. Multivariate analysis showed that perioperative transfusion of FFP was less frequent in women receiving HRT than in women not receiving HRT, and that men had a significantly lower incidence of postoperative CHF than did women not receiving HRT.

Several large, prospective, randomized, controlled clinical trials have failed to show significant protective cardiovascular effects of long-term HRT on women with or without known coronary artery disease. The Heart and Estrogen/Progestin Replacement (HERS) study,[8,10] the Estrogen Replacement and Atherosclerosis (ERA) trial,[9] and the Women's Health Initiative (WHI) study[11-13] showed no significant benefit and small but significant increases in the risk of adverse coronary events. The latest American Heart Association recommendations state that estrogen with or without progesterone should not be initiated or continued in postmenopausal women if the primary objective is preventing cardiovascular disease.[19]

It is known, however, that estrogen has protective effects on the cardiovascular system.[17] In animal mod-

els of vascular injury, estrogen inhibits neointimal formation and subsequent thrombosis.[20-27] In addition, the inflammatory response to the reperfusion of ischemic tissues is altered by estrogen.[28,29] In human females, the effects of estrogen on endothelial and vascular smooth-muscle cells modulate the vascular response to stress.[30-32] In postmenopausal women, estrogen has been shown to improve myocardial blood flow[33] and reduce pacing-induced myocardial ischemia.[34] One study has found that acute intracoronary administration of estrogen (Premarin, Wyeth; Madison, NJ) in women or men undergoing angioplasty rendered the heart resistant to the ischemia caused by the procedure.[35] Finally, acute postoperative transdermal administration of 17β-estradiol to a group of CABG patients induced a significant increase in postoperative left IMA graft diameter.[36]

The results of some clinical studies have supported the potentially beneficial effects of estrogen for patients undergoing cardiovascular procedures. Postmenopausal women undergoing elective percutaneous transluminal coronary angioplasty or stenting had longer survival[16] or less need for repeat revascularization[17] if they were receiving HRT. Sullivan and coworkers[7] studied 1,098 postmenopausal women undergoing CABG and found that, although only 92 women (8.4%) were receiving HRT at the time of CABG, they had a 5-year survival rate of 98.8% compared with a rate of 82.3% in estrogen non-users. The 10-year survival rates were 81.4% and 65.1%, respectively. In a multivariate analysis of long-term survival after CABG, HRT remained significantly beneficial.

Two recent single-center studies of CABG patients aged 55 years or more showed that women receiving preoperative HRT had a lower in-hospital mortality rate than did women who were not receiving HRT.[5,6] Shackelford and colleagues[6] retrospectively studied 734 consecutive postmenopausal women undergoing isolated CABG from 1992 to 1997, of whom 102 (13.9%) received estrogen. Univariate analysis showed that the perioperative mortality rate was significantly lower in the women receiving HRT (2.7% vs 7.4%), although stepwise logistic regression failed to confirm that HRT was a significant predictor of lower mortality. More recently, Nussmeier and colleagues[5] studied 4,259 consecutive patients aged 55 years or older who were undergoing isolated CABG. Female sex independently predicted mortality among 905 women without HRT (6.7%) (P <0.05), but not among 256 women receiving HRT (2.3%), compared with the mortality in 3,098 men (2.3%).

The findings of the current multicenter study are similar to those of the single-center studies. Although stepwise logistic regression failed to confirm that HRT was protective against death or any other adverse outcome, there were no apparent risks associated with HRT use before cardiac surgery. Generally, the women receiving HRT experienced outcomes similar to those of men. On the other hand, although the women not receiving HRT had worse outcomes than did the men, those women were significantly older and were less likely to receive an IMA graft (with its associated benefits) than were either the men, or the women receiving HRT. These factors have been shown to affect survival and other outcomes in previous studies, independent of sex.[37,38] Therefore, it is not surprising that multivariate analysis did not confirm a benefit of HRT.

Finally, among CABG patients, the transfusion of blood products is known to be more common in women than in men, possibly contributing to women's higher morbidity rate after CABG.[39-41] Estrogen is as effective as 2 units of FFP in correcting prolonged bleeding in patients undergoing renal transplantation[42] and has been noted to significantly decrease the use of FFP, platelets, and RBCs in patients undergoing liver transplantation.[43] Although the mechanism of estrogen's action in reducing bleeding is unknown, these findings are consistent with our results.

A major limitation of the current investigation is the purely observational study design. Because HRT was not randomly assigned, its effects may have been confounded by treatment bias; for example, the women using HRT may have been healthier than those not using HRT.[44] Other limitations include the relatively small proportion of women undergoing CABG (20% in the present study) and, of these, the small percentage currently receiving HRT (only 15%), which is slightly lower than the 20% estrogen-use rate reported by the National Center for Health Statistics.[45] These small numbers decreased the study's statistical power to detect differences in outcomes. In addition, the specific HRT drug and dosing regimen were not standardized, and our data do not indicate whether previous HRT had been recent or remote. Finally, because the institutions participating in the current study did not use a consistent algorithm to make decisions regarding blood transfusions, it was difficult to assess the effect of HRT on transfusion requirements. These limitations could potentially be overcome in a large, prospective, randomized study of perioperative administration of estrogen to women undergoing CABG, with examination of the effects of this drug on cardiovascular outcomes, transfusion requirements, and the inflammatory response to surgery and cardiopulmonary bypass.

Conclusion

We conclude that women taking HRT should not discontinue therapy before CABG. Whether patients receiving HRT should continue to take their medication after hospital discharge has yet to be determined.

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Appendix

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